REMARKS

Previously pending claims 55-57, 59-68, 70-72, 74-88, 90-94, 102-104 and 109-116 have been cancelled and new claims 117-141 have been added. Support for the amendments can be found in the specification and in the original claims as filed. No new matter has been added.

Claims 117-130 and 141 are directed to the originally elected subject matter of a genetically modified or transgenic mouse.

Claims 131-133 are directed to a cell isolated from the transgenic mouse. Claims 134-137 are directed to methods of screening compounds and studying heart failure utilizing the transgenic mouse. Claims 138-140 are directed to a method for creating the transgenic mouse.

CLAIM REJECTIONS - 35 USC § 112, FIRST PARAGRAPH

At page 2, the Office Action rejects claims 55-57, 59-68 and 110-116 under 35 U.S.C. § 112, first paragraph, enablement requirement. Applicants respectfully traverse the rejection.

Claims 55-57, 59-68 and 110-116 have been cancelled and new claims 117-141 have been added. Claims 117-130 and 141 are directed to the elected subject matter under examination.

Claim 117 is directed to a transgenic mouse whose genome comprises a homozygous disruption in an endogenous Serca2 gene in heart cells following expression of a site-specific

recombinase of heterogenous origin. The disruption of the Serca2 gene results in a lack of expression of a functional Serca2 protein in the heart cells.

The Office Action acknowledges that the specification enables a transgenic mouse in which both endogenous genomic copies of the Serca2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter. The Office also recognizes that following the expression of Cre recombinase in heart cells, both copies of the endogeneous Serca2 gene are disrupted.

The Office Action contends that the specification does not reasonably enable a transgenic mouse in which any genomic Serca ATPase gene has recombination sites inserted in both gene copies. The present claims, however, are limited to a transgenic mouse with homozygous disruption in the Serca2 gene.

In addition, the Office appears to hold the position that the specification fails to teach one of skill in the art how to use the invention as claimed. As featured in the present claims, the disruption of Serca2 results in a lack of expression of functional Serca2 protein in the heart cells. Claim 118 further defines the effects of Serca2 disruption as defective Ca^{2+} handling, reduced Ca^{2+} pumping ability, decreased heart contractility and heart failure.

In view of the amendments and the above remarks, the specification supports the full scope of present claims 117-130 and 141, as required by 35 U.S.C. § 112, first paragraph. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTIONS - 35 USC § 112, SECOND PARAGRAPH

At page 10, the Office Action rejects claim 56 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse the rejection.

Claim 56 has been cancelled, thus obviating the rejection. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTIONS - 35 USC § 103

At page 11, the Office Action rejects claims 55-57 and 59-68 under 35 U.S.C. § 103(a) as being unpatentable over PERIASAMY et al. (J. Biol. Chem. (1999) Vol. 274(4), 2556-2562) in view of SOHAL et al. (Circ. Res. (2001) Vol. 89, 20-25). Applicants respectfully traverse the rejection.

Claims 55-57 and 59-68 have been cancelled and new claims 117-130 and 141 are directed to the elected subject matter under examination.

Present claim 117 is directed to a transgenic mouse whose genome comprises a homozygous disruption in an endogenous

Serca2 gene in heart cells following expression of a site-specific recombinase of heterogenous origin. The disruption of the Serca2 gene results in a lack of expression of a functional Serca2 protein in the heart cells. The transgenic mouse can be used as animal model to study defective Ca^{2+} handling, reduced Ca^{2+} pumping ability, decreased heart contractility and heart failure. The combination of PERIASAMY and SOHAL fails to teach or suggest such a transgenic mouse.

PERIASAMY investigates the function of the SERCA2 gene in heart disease by creating a SERCA2 knockout mouse. PERIASAMY, however, teaches away from a homozygous mutant SERCA2 knockout mouse. Right away, PERIASAMY observed that they were not able to obtain homozygous SERCA2 mutants. Thus, PERIASAMY found it necessary to perform their studies on heterozygous animals. PERIASAMY recognized that "homozygous mutants would not survive" and that it would be necessary to perform their studies on heterozygous mutants. PERIASAMY further discloses that because homozygous mutants were not observed, "one or both variants of SERCA2 serve functions that are essential for life, and that other pumps cannot provide sufficient compensation to rescue the null mutant." (see, page 2560, Discussion, first paragraph, emphasis added).

Beyond these observations, PERIASAMY does not comment any further on the homozygous mutants, and as mentioned, continued its studies on heterozygous mutants. In these mice,

PERIASAMY demonstrated a ~35% reduction in SERCA2a levels and Ca^{2+} uptake activity along with measured physiological effects on arterial blood pressure and left ventricular systolic pressure. The adult mice (12-16 weeks), however, were healthy with no evidence of heart disease (see, page 2562, first full paragraph).

Finally, PERIASAMY concludes that the reduction in Ca^{2+} sequestering activity, resulting from loss of one copy of the SERCA2 gene, is not a sufficient pertubation to cause heart disease in adult mice. PERIASAMY then states "it remains to be determined whether heterozygous mutants may be more prone to heart disease as they age." (See, page 2562, end of first full paragraph).

Thus, from the teachings of PERIASAMY, one of ordinary skill in the art would determine that (1) homozygous mutants of SERCA2 are lethal, (2) heterozygous mutants of SERCA2 do not exhibit observable physiological effects and (3) the mice do not develop heart disease even after 112 days.

After mentioning that SERCA2 homozygous mutants could not be developed, PERIASAMY is silent on any further strategy for developing homozygous mutants. PERIASAMY also fails to teach or suggest that homozygous mutants would develop any physiologically observed heart disease.

The Office Action states that PERIASAMY was cited "for providing motivation for determining the effects of a complete loss of SERCA2 on adult cardiac function." (See, page 12 of the

Office Action). Applicants respectfully disagree with this conclusion. The Office fails to provide any logic for why PERIASAMY allegedly provides this motivation for creating homozygous null mutants. Indeed, PERIASAMY is completely silent on this aspect and even teaches away from homozygous SERCA2 mutants. PERIASAMY fails to provide any motivation for a homozygous knockout mouse as a model for studying heart disease.

Applicants also provide a Rule 132 Declaration of Dr. Frank Wutack, an expert in the field of molecular and cell biology and in the subject of Ca^{2+} transport ATPase enzymes. The declaration provides further evidence that at the time of invention of the presently claimed subject matter, one of ordinary skill in the art would have considered SERCA2 to be critical for life, both at the embryonic stage and at the adult stage. One would not have expected a homozygous SERCA2 knockout mouse to survive beyond about one week. The presently claimed transgenic mice unexpectedly survived more than 5 weeks before developing heart pathology as adults.

The Office Action cites SOHAL for teaching that the embryonic, fetal, or neonatal lethality observed in some homozygous knockout mice, which prevents assessment of target gene function in the neonatal or adult heart, can be circumvented by the use of an inducible and tissue specific Cre-Lox system. The Office Action concludes that it would have been obvious to

use the system of SOHAL to generate a homozygous SERCA2 knockout mouse. Applicants respectfully disagree with this conclusion.

As verified in the Rule 132 Declaration of Dr. Wuytack, SERCA2 encodes a protein, which at the time of filing of the present application, was assumed to be essential for life during the embryonic phase and in adult mice. PERIASAMY states that SERCA2, more specifically the SERCA2a isoform, plays a central role in cardiomyocyte Ca^{2+} handling (see, page 2556, left column, second paragraph) and that reduced levels of SERCA2a is a factor in heart disease (page 2562, bottom paragraph). On these grounds, PERIASAMY projected that homozygous SERCA2 mutant would not survive and that it would be necessary to perform the studies on heterozygotes (see, page 2560, discussion, first paragraph).

One of ordinary skill in the art would expect that a homozygous SERCA2 deletion, once induced, would be instantly lethal in adult mice. Such an animal model would serve no purpose and one would be led away from producing such a genetically modified mouse as defined in the present claims. Contrary to these expected results, and as detailed in the present specification, Applicants surprisingly found that homozygous SERCA2 deletion mutants survived for more than 50 days after induction of the deletion. Thus, the deletion mutant survival window is far wider than one of ordinary skill would have expected and renders a heart failure model possible.

For all of these reasons, PERIASAMY and SOHAL fail to teach or suggest, and would not have rendered obvious, claims 117-130 and 141. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item:

- a 37 CFR 1.132 Declaration of Dr. Frank Wuytack